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A Phase I/II Trial of TG01 and Gemcitabine as Adjuvant Therapy for Treating Patients with Resected Adenocarcinoma of the Pancreas

Targovax ASA Study No: CT TG01-01

Statistical Analysis Plan

Version: Amendment 1.0 Final 1.0

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For Targovax ASA

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Contents

ABBREVIATIONS

Abbreviation	Term
5-FU	5-Fluorouracil
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	All treated patients
BUN	Blood urea nitrogen
CI	Confidence Interval
CK	Creatinine kinase
CRF	Case Report Form
DFS	Disease-free survival
DLT	Dose-limiting toxicity
DTH	Delayed Type Hypersensitivity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
GM-CSF	Granulocyte macrophage colony stimulating factor
IA	Interim analysis
IAS	Immune analysis set
IMP	Investigational medicinal product
INR	International normalised ratio
ITT	Intention-to-treat
KRAS	Kirsten rat sarcoma viral oncogene homolog
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MIAS	Modified Immune analysis set
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
OS	Overall survival
PP	Per-protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SI	Stimulation Index
SOC	System Organ Class

TEAE	Treatment-emergent Adverse Event
TFL	Tables, figures and listings
UNL	Upper Normal Limit
WHODrug	World Health Organization Drug dictionary

1   INTRODUCTION

This document details the statistical analysis of the data that will be performed for the Targovax ASA study: A Phase I/II Trial of TG01 and Gemcitabine as Adjuvant Therapy for Treating Patients with Resected Adenocarcinoma of the Pancreas.

This Statistical Analysis Plan (SAP) is based on protocol final version 9.0 dated 27 June 2016. In the event of future amendments to the protocol, this statistical analysis plan (SAP) may be modified to account for changes relevant to the statistical analysis.

The table, listing and figure shells (TFLs) will be supplied in a separate document but form part of the complete SAP document.

2   GENERAL PRINCIPLES

The analysis and statistics reporting will be conducted at ▇▇▇▇▇▇▇▇ using SAS version 9.2 or higher.

All listings will be based on all treated patients unless specified otherwise.

Listings and figures will be presented by Main group, Concomitant group and Modified vaccination group. Tables will be presented by Main group, Concomitant group, Main + Concomitant, Modified vaccination group separately unless otherwise specified and Overall (Main + Concomitant + Modified vaccination).

Descriptive summary statistics for continuous variables will include the number of patients (n), mean, standard deviation (SD), median, interquartile range, minimum and maximum unless specified otherwise. The precision of these summary statistics is defined in the TFL shells document.

Descriptive summary statistics for categorical variables will include frequency counts and percentages [n (%)]. In general, the denominator for percentage calculations will be the number of patients in the analysis set. However, for tables by time point the percentages will be calculated using the number of patients with available data at that time point.

3   STUDY OBJECTIVES AND DESIGN

3.1 Study Objectives

The primary objectives of the study are:

- To assess the safety of GM-CSF/TG01 vaccination and adjuvant chemotherapy.

- To assess the immune response to GM-CSF/TG01 and the effect of adjuvant chemotherapy in patients receiving GM-CSF/TG01 after primary resection of pancreatic adenocarcinoma.

The secondary objective of this study is:

- To assess at 2 years the clinical efficacy of GM-CSF/TG01 in patients with resected pancreatic cancer.

The exploratory objectives of the study are:

- To assess the relationship of Kirsten rat sarcoma viral oncogene homolog (KRAS) status to recurrence.

- Monitor CA19-9 levels.

3.2 Study Design

This is a Phase I/II trial of TG01 and gemcitabine as adjuvant therapy for testing patients with resected adenocarcinoma of the pancreas. Patients will be enrolled in 5 study centre(s) and the study duration will be approximately 5 years.

Phase I part

The phase I part of the study will be initiated with 6-12 patients enrolled within 1-8 weeks after surgery to receive GM-CSF given 10-15 minutes before TG01. Gemcitabine will be started at least 3 weeks after the initiation of immunotherapy but not later than 12 weeks after surgery. Note that, in some centres where transaminases are > 2.5 x Upper Limit of Normal Limit (UNL) at the time of chemotherapy, 5-FU/Leucovorin may be substituted. However, the number of patients in the study refers to those receiving gemcitabine and therefore, for every patient who receives 5-FU only rather than gemcitabine, a further patient will be added.

Initially 6 patients will be treated with GM-CSF/TG01 within 1-8 weeks after surgery and when these 6 patients have reached Week 11:

- If 0/6 patients have an immune response and/or there are >3/6 patients with GM-CSF/TG01 related dose-limiting toxicities (DLTs) observed, the study will be terminated.

- If 1-3/6 patients have an immune response and/or if there are ≤3/6 patients with GM-CSF/TG01 related DLTs observed, 6 new patients will be enrolled and will be treated in the same way as the previous patients.

- If ≥ 4/6 patients have an immune response and ≤ 2/6 patients have a GM-CSF/TG01 related DLT, the phase II study will be initiated.

If the enrolment of the phase I part is expanded to 12 patients, then at Week 11:

- If < 4/12 patients have an immune response and/or there are > 4/12 patients with GM-CSF/TG01 related DLTs, the study will be terminated.

- If ≥ 4/12 patients have an immune response and ≤ 4/12 patients have a GM-CSF/TG01 related DLT, the phase II study will be initiated.

Phase II part

A further 18-25 patients treated with GM-CSF/TG01 + Gemcitabine will be added in the Phase II part of the study to provide a total of up to 32 patients in the study as a whole.

This Phase II part will comprise 3 groups of patients:

- Main group (phase I and phase II) – Patients starting vaccination and receiving chemotherapy later. Treatment schedule is described in Figure 3: "Treatment

schedule for patients starting vaccination and receiving chemotherapy later – Main group" of the protocol.

- Concomitant group (phase II) – Patients starting vaccination and chemotherapy at the same time, maximum 6 patients. Treatment schedule is described in Figure 4: "Treatment schedule for patients starting vaccination and chemotherapy at the same time – concomitant group" of the protocol.

- Modified vaccination group (phase II) – Patients starting vaccination according to a modified schedule of administration of GM-CSF/TG01 and receiving chemotherapy later, up to 13 patients. Treatment schedule is described in Figure 5: "Treatment schedule for patients starting vaccination and receiving chemotherapy later – Modified vaccination group" of the protocol.

Patients who are withdrawn for reasons other than toxicity may be replaced if they received less than 4 weeks of vaccination and have not started gemcitabine.

3.3 Visit Structure

Patients will be assessed according to the visit schedules described in Table 1: Schedule of Visits, Table 2: Schedule of Visits – Concomitant group, and Table 3: Schedule of Visits – Modified vaccination group of the protocol.

3.4 Sample Size

No formal sample size has been calculated. Six to 12 patients in the Phase 1 part of the study and up to 32 patients in total in the study are deemed sufficient to assess the safety and immune response in this pilot study and will give an early indication of efficacy in terms of disease-free survival (DFS) and overall survival (OS) when compared to historical controls (Oettle 2007 and Neoptelemos 2010).

3.5 Changes from the Protocol Planned Analysis

Section 6.3 of the protocol refers to intention-to-treat (ITT) and per-protocol (PP) populations. These have been replaced throughout the SAP by All Treated Patients (ATP) analysis set and Modified Immune analysis set (MIAS) respectively.

Sections 5.8.2 and 5.8.3 of the protocol define DFS and OS respectively as time from randomisation, but patients are not randomised in this study. Therefore, in the SAP (section 6.2.1 and 6.2.2) this is changed to separate analyses for time from first administration of Investigational medicinal product (IMP) and time from surgery.

Section 6.3.2.4 of the protocol refers to other biomarkers. For now, these biomarkers have not been identified, and no summary statistics are planned in this SAP.

The DFS, OS and CA19-9 analyses will be repeated for the subgroup of patients who received Gemcitabine only.

3 years survival estimates will be presented for DFS and OS for the main and concomitant groups.

4 STUDY PATIENTS

4.1 Analysis Sets

Assignment of patients to analysis sets will be agreed between the study statistician and the Sponsor prior to database lock, once all study data are available and verified.

All Treated Patients (ATP): Defined as those patients who receive at least one dose of IMP which is either TG01, GM-CSF, gemcitabine or 5-FU/ Leucovorin. This analysis set will be used to assess the safety and survival endpoints.

Immune Analysis Set (IAS): Defined as those patients who provide at least one set of T cell and/or delayed type hypersensitivity (DTH) response results.

Modified Immune Analysis Set (MIAS): Defined as all patients in the IAS who have received at least one cycle of gemcitabine or 5-FU/leucovorin.

Assessment of the immune response endpoint will be based on the IAS and MIAS. The MIAS will serve as the primary analysis set for the assessment of immunology data whereas the IAS will be considered the secondary analysis set.

All treated patients will be listed indicating their eligibility to IAS and MIAS and reasons for exclusion from these analysis sets as appropriate.

4.2 Disposition of Patients

The following patient disposition details will be summarised and will include the number and percentage of patients:

- included in each analysis set (ATP, IAS and MIAS)
- who completed the study
- who prematurely withdrew (including a breakdown of the primary reasons for withdrawal)

Individual reasons for withdrawal will be presented in the listing for all treated patients.

4.3 Eligibility

All responses to the inclusion and exclusion criteria will be listed including a column detailing which protocol version the patient entered the study.

In a separate listing all pregnancy test results and details will be presented.

4.4 Protocol Deviations

Details of all protocol deviations (start and end dates, deviation category and specific details) will be listed.

4.5 Demographic and other Baseline Characteristics

Summaries of demographic and other baseline characteristics will be based on the ATP analysis set.

4.5.1 Demography

Demographic characteristics (age, sex and race) and body measurements (height and weight collected at Screening) will be summarised.

Age will be calculated in years from the date of birth to the date of informed consent.

Individual patient demographic and body measurement data recorded at Screening will be listed, consent date will also be presented.

4.5.2 Medical History of Pancreatic Cancer and KRAS Mutation Analysis

The number and percentage of patients with KRAS mutation detected (yes/no) and by mutation type (codon12/13, codon 61, other) will be presented. Percentages will respectively be based on the number of patients with tumour sample retained for KRAS status determination and the number of patients with KRAS mutation detected.

Descriptive summary statistics will be presented for time from diagnosis to first IMP administration (weeks), time from diagnosis to surgery (weeks) and time from surgery to first IMP administration (weeks). The number and percentage of patients by disease staging at diagnosis and resection surgery outcome will be also be displayed.

Time from diagnosis to first IMP administration (weeks) is calculated as (date of first IMP administration – date of diagnosis + 1) / 7 rounded to 1 decimal place.

Time from diagnosis to surgery (weeks) is calculated as (date of surgery – date of diagnosis + 1) / 7 rounded to 1 decimal place.

Time from surgery to first IMP administration (weeks) is calculated as (date of first IMP administration – date of surgery + 1) / 7 rounded to 1 decimal place.

All pancreatic cancer medical history details will be listed along with KRAS status if a tumour sample was taken for KRAS status determination.

In a separate listing the KRAS mutation analysis details will be presented.

4.5.3 Medical History (Excluding Resected cancer)

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 15.1 or higher.

The number and percentage of patients with current medical history events, defined as those recorded as 'ongoing' on the eCRF will be tabulated by system organ class (SOC), preferred term (PT) for each group. SOCs will be ordered in decreasing frequency of the total number of patients with current medical histories reported in each SOC and PTs will be ordered within a SOC in decreasing frequency of the total number of patients with each current medical history. This summary will be repeated for past medical history events, defined as those not recorded as 'ongoing' on the eCRF.

All medical history events (excluding resected pancreatic cancer) will be listed by SOC and PT.

4.5.4 Prior and Concomitant Medication

Concomitant medications will be coded according to the World Health Organization Drug dictionary (WHODrug) (Standard) version of September 2012 or later.

Prior medications are defined as those for which the end date is prior to the date of first IMP administration.

Concomitant medications are defined as those which are indicated as 'Ongoing' on the date of first IMP administration, or those which start on or after the date of first IMP administration, or those which start prior to date of first IMP administration and have an end date after the first IMP administration.

If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

The number and percentage of patients who took any concomitant medications will be presented by medication class and standardised medication names sorted alphabetically.

All prior and concomitant medications will be listed by reported name, medication class, standardised medication name, indication, dose, dose unit, frequency, route of administration, start date and end date or 'ongoing' flag. Concomitant medications will be flagged. All medications which start up to four weeks prior to first dose of IMP will also be flagged in the listings.

4.5.5 Prophylaxis

Prophylaxis medication will be coded according to the WHODrug (Standard) version of September 2012 or later.

The number and percentage of patients who had any prophylaxis medications will be presented by medication class and standardised medication names sorted alphabetically.

All prophylaxis medications will be listed by reported name, medication class, standardised medication name, indication, dose, dose unit, frequency, route of administration, start date and end date or 'ongoing' flag.

4.6 Investigational Medicinal Product Administration

All details of GM-CSF/TG01 administration will be listed alongside with TG01 administration for DTH test details, including derived variables as described in Section 5.1.

The gemcitabine administration details will be listed separately from the 5-FU/leucovorin administration details.

5 SAFETY EVALUATION

All safety evaluations will be performed on the ATP analysis set.

Adverse events and laboratory values collected during the study are the primary safety endpoints of interest.

Unscheduled laboratory samples or clinical evaluations may be taken if parameters are out of range. Results from unscheduled samples and assessments will be listed but will not be included in the summaries described below.

5.1 Study Drug Exposure

5.1.1 GM-CSF/TG01

The duration of exposure to GM-CSF/TG01 in days, as well as the total dose of GM-CSF and the total dose of TG01 separately for vaccination, DTH testing, and vaccination and DTH testing combined will be summarised.

Duration of exposure to GM-CSF/TG01 will be calculated as: date of last GM-CSF/TG01 administration – date of first GM-CSF/TG01 administration + 1.

Total dose of GM-CSF will be calculated as: sum of administered dose (dose strength*volume) at each visit.

Total dose of TG01 for DTH testing will be calculated as: sum of administered dose (dose strength*volume) for DTH test at each visit.

Total dose of TG01 for vaccination will be calculated as: sum of administered dose (dose strength*volume) for vaccination at each visit.

Total dose of TG01 for vaccination and DTH testing combined will be calculated as: sum of administered dose (dose strength*volume) for vaccination at each visit + sum of administered dose (dose strength*volume) for DTH test at each visit.

The number of injections of GM-CSF/TG01, number of injections of TG01 for DTH test, and total number of injections (GM-CSF/TG01 + DTH) will be summarized overall and for the following periods: before chemotherapy, during chemotherapy, and after chemotherapy.

The number and percentage of patients with dose delays and discontinuation for GM-CSF/TG01, together with the frequency and reasons for such dose modifications, will be summarised by visit and overall.

5.1.2 Gemcitabine

The duration of exposure to Gemcitabine in days, as well as the number of cycles, number of injections of Gemcitabine and the total dose of Gemcitabine will be summarised.

Duration of exposure to Gemcitabine will be calculated as: date of last Gemcitabine administration – date of first Gemcitabine administration + 1.

Total dose of Gemcitabine will be calculated as: sum of administered dose at each injection.

The number and percentage of patients with dose delays, reductions and discontinuation for Gemcitabine, together with the frequency and reasons for such dose modifications, will be summarised by cycle and overall.

5.1.3 5-FU/Leucovorin

The duration of exposure to 5-FU/Leucovorin in days, as well as the number of cycles, number of injections of 5-FU/Leucovorin and the total dose of 5-FU/Leucovorin will be summarised.

Duration of exposure to 5-FU/Leucovorin will be calculated as: date of last 5-FU/Leucovorin administration – date of first 5-FU/Leucovorin administration + 1.

Total dose of 5-FU/Leucovorin will be calculated as: sum of administered dose at each injection.

The number and percentage of patients with dose delays, reductions and discontinuation for 5-FU/Leucovorin, together with the frequency and reasons for such dose modifications, will be summarised by cycle and overall.

5.2 Adverse Events

Any events that are unequivocally due to progression of disease will not be reported as adverse events (AEs) or serious AEs (SAEs).

AEs will be coded according to MedDRA version 15.1 or higher.

A treatment-emergent adverse event (TEAE) is defined as an AE with start date/time on or after the first administration of IMP, or AEs with worsening severity on or after the first administration of IMP. A pre-treatment AE is defined as an AE with start date/time prior to the first administration of IMP.

AEs with unknown start date/time will be assumed to be treatment-emergent unless the end date/time is known to be before the first administration of IMP.

Assessment of AE severity will be based on the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.0) graded as 1-5 grades, with grade 5 being death. For AEs that cannot be assessed based on the NCI-CTCAE, severity will be assessed as mild, moderate, severe or life-threatening. In summary tables, severity will be grouped as grade 1/mild, grade 2/moderate, grade 3/severe, grade 4/life threatening, and grade 5. If the severity of an event changes during the course of that event, only the maximum severity / grade will be summarised in the tables.

The relationship to each IMP (TG01, GM-CSF, Gemcitabine, 5-FU and Leucovorin) is assessed as not related or related.

An overview summary table will summarise the number of events and the number and percentage of patients with at least one of the following TEAES:

- total TEAEs

- total serious TEAEs

- total IMP related serious TEAEs

- total DLTs

- TEAEs leading to TG01 and GM-CSF withdrawal

- TEAEs leading to Gemcitabine, 5-FU or Leucovorin withdrawal

- TEAEs leading to study withdrawal

- TEAEs leading to death

- TEAEs by severity

- TEAEs by relationship to each IMP (related, not related) separately

The number of events and the number and percentage of patients experiencing TEAEs will be presented by SOC and PT. SOC and PT will be presented in decreasing

frequency of the total number of patients with TEAEs. If a patient experienced more than one TEAE, the patient will be counted once for each SOC and once for each PT. Serious TEAEs will be summarized in an identical fashion.

The number of events and the number and percentage of patients experiencing TEAEs that are DLTs will be presented by SOC and PT. SOC and PT will be presented in decreasing frequency of the total number of patients with TEAEs. If a patient experienced more than one TEAE considered to be DLT, the patient will be counted once for each SOC and once for each PT.

The number of events and the number and percentage of patients experiencing TEAEs will be presented by SOC, PT and severity. SOC and PT will be presented in decreasing frequency of the total number of patients with TEAEs. If a patient experienced more than one TEAE, the patient will be counted once for each severity experienced during the study.

The number of events and the number and percentage of patients experiencing TEAEs will be presented by SOC, PT and relationship to each IMP. SOC and PT will be presented in decreasing frequency of the total number of patients with TEAEs. If a patient experienced more than one TEAE, the patient will be counted once for each SOC and once for each PT at the closest relationship to study drug. This summary will be repeated for serious TEAEs only.

The number of events related to TG01 and the number and percentage of patients experiencing TEAEs related to TG01 will be presented by SOC, PT and severity. For this table, grade 1 and 2 events will be pooled. SOC and PT will be presented in decreasing frequency of the total number of patients with TEAEs. If a patient experienced more than one TEAE, the patient will be counted once for each severity experienced during the study. TEAEs related to GM-CSF, TEAEs related to TG01 and/or GM-CSF and TEAEs related to TG01 and/or GM-CSF only (i.e., events not related to chemotherapy) will be summarized in an identical fashion.

All TEAEs details will be listed with a separate listing for pre-treatment AEs.

Separate listing of all serious TEAEs and pre-treatment SAEs will also be presented.

5.3 Deaths

The total number and percentage of patients who died whilst on the study will be summarised and by cause of death (due to the patient's disease or AE).

The statement of death details will be listed presenting date of death, primary and secondary cause of death, whether the death was related to the patient's disease or related to an AE and whether an autopsy was performed.

5.4 Clinical Laboratory Evaluation

Data for haematology, biochemistry, urinalysis and clotting screen parameters will be received from laboratories local to the trial centres. Parameters will be tabulated and listed in the order shown in Table 1. International Normalized Ratio (INR) will be presented with the biochemistry parameters.

For each laboratory parameter, the baseline value will be defined as the last scheduled or unscheduled value collected prior to first dose of IMP. Assessments carried out on day of first IMP administration are considered to have taken place before the IMP

administration, if the corresponding times have not been recorded. For post baseline, only data from scheduled visits will be included in the summary tables. Percent change from baseline will be calculated as 100 * (observed value – baseline value) / baseline value.

Conversion factors will be applied where needed to report all laboratory results using the international system of units.

Table 1:

Haematology	Biochemistry	Urinalysis Dipstick	Clotting Screen
Red blood cell count/erythrocytes	Alkaline phosphatase	Blood	INR
Haemoglobin	ALT (SGPT)	Protein	
Haematocrit	AST (SGOT)	Glucose	
White blood cell count/leucocytes	Total protein	White cells	
Neutrophils	Albumin		
Lymphocytes	Bilirubin		
Monocytes	Lactate dehydrogenase (LDH)		
Eosinophils	Blood urea nitrogen (BUN)		
Basophils	Creatinine		
Platelet count	Sodium		
	Potassium		
	Creatinine kinase (CK)		

5.4.1   Haematology

Haematology values will be summarised by parameter and visit, including change from baseline and percent change from baseline.

The number and percentage of patients with low (clinically significant), low (not clinically significant), normal, high (not clinically significant), high (clinically significant), missing and total results based on reference ranges will be summarised by parameter and visit. Patients will only be included in the missing and total categories if they attended the visit but have no data available for that parameter. Patients who withdrew prior to the visit will not be included in the summary for that visit, and will be excluded from the denominator for calculation of percentages at that visit.

Individual patient haematology values up to 1 year after first dose of IMP will be plotted, with separate pages for each group and parameter. Additionally, box plots will be produced to summarize values over time, with separate pages for each group and parameter.

All haematology values will be listed showing reference ranges and flagging all abnormal findings and their clinical significance. Out of reference range values will be flagged as high (H) or low (L).

5.4.2   Biochemistry including INR

Biochemistry and INR values will be summarised by parameter and visit, including change from baseline and percent change from baseline.

The number and percentage of patients with low (clinically significant), low (not clinically significant), normal, high (not clinically significant), high (clinically significant), missing and total results based on reference ranges will be summarised by parameter and visit. Patients will only be included in the missing and total categories if they attended the visit but have no data available for that parameter. Patients who withdrew prior to the visit will not be included in the summary for that visit, and will be excluded from the denominator for calculation of percentages at that visit.

Individual patient biochemistry values up to 1 year after first dose of IMP will be plotted, with separate figures for each group and parameter. Additionally, box plots will be produced to summarize values over time, with separate pages for each group and parameter.

All biochemistry values will be listed showing reference ranges and flagging all abnormal findings and their clinical significance. Out of reference range values will be flagged as high (H) or low (L).

5.4.3   Urinalysis

All urinalysis dipstick results will be listed.

5.5 Vital Signs

Vital signs include weight, pulse rate, systolic blood pressure, diastolic blood pressure and body temperature. Vital sign values will be summarised by parameter and visit, including change from baseline and percent change from baseline. For each parameter, the baseline value will be defined as the last scheduled or unscheduled value collected prior to first dose of IMP. Assessments carried out on day of first IMP administration are considered to have taken place before the IMP administration, if the corresponding times have not been recorded. For post baseline, only data from scheduled visits will be included in the table. Percent change from baseline will be calculated as 100 * (observed value – baseline value) / baseline value.

All vital signs values will be listed, flagging any unscheduled assessments.

5.6 Electrocardiogram (ECG)

All ECG data will be listed, flagging any unscheduled ECG assessments.

5.7 Physical Examination and Eastern Cooperative Oncology Group (ECOG) Performance Status

The number and percentage of patients by ECOG status and visit will be tabulated and a shift table will present shift from baseline in ECOG status by visit. The baseline value will be defined as the last scheduled or unscheduled value collected prior to first

dose of IMP. Assessments carried out on day of first IMP administration are considered to have taken place before the IMP administration, if the corresponding times have not been recorded. For post baseline, only data from scheduled visits will be included in the tables. Patients who attended a visit but have no ECOG data available will be included in the missing and total categories. Patients who withdrew prior to the visit will not be included in the summary for that visit, and will be excluded from the denominator for calculation of percentages at that visit.

A listing will present ECOG assessment date and ECOG performance status together with whether the physical examination was performed and the date of examination.

6   EFFICACY EVALUATION

6.1   Immune Response

To assess the immune response to GM-CSF/TG01 (one of the primary objectives of the study), the primary efficacy endpoint is the proportion of patients with an immune response by Week 11 or 12 (main group) or by Week 13 (concomitant group) or by Week 8 (modified vaccination group). The proportion of patients with an immune response by at the end of the treatment period with chemotherapy, at Week 52 and at end of study will also be presented.

6.1.1   Derivation rules

An immune response is defined as having a positive DTH skin reaction and/or a positive T-cell response at least once by the end of the initial treatment period (Week 11 or 12 in main group, Week 13 in concomitant group, Week 8 in modified vaccination group) excluding Day 1, at the end of the treatment period with chemotherapy, at Week 52 and at end of study.

The DTH test is considered positive if erythema and/or induration are recorded as positive on the DTH response eCRF page.

A patient is considered to have a positive T-cell response if the stimulation index (SI) is ≥ 2.

The SI will be derived as follows:

$$\frac{\text{Mean (T cells } + \text{ PBMC} + \text{TG01})}{\text{Mean (T cells } + \text{ PBMC (negative control))}}$$

For SI, mean is derived as the sum of the non-missing measurements divided by the number of non-missing measurements, rounded to the nearest whole number.

6.1.2   Endpoint summaries

Where applicable, each summary will use the number of patients with data at that time point as the denominator for the calculation of percentages.

The number and percentage of patients with an immune response by Week 11 or 12 (main group) or by Week 13 (concomitant group) or by Week 8 (modified vaccination group), at the end of the treatment period with chemotherapy, at Week 52, at end of study, and over the entire study course will be presented for the MIAS as the primary analysis. This will be repeated for the IAS as a secondary analysis.

A summary of the number and percentage of patients with at least one positive DTH skin reaction by Week 11 or 12 (main group) or by Week 13 (concomitant group) or by Week 8 (modified vaccination group), at the end of the treatment period with chemotherapy, and at Week 52 (main and concomitant groups only) will be presented for both the MIAS and IAS.

On a separate table the number of positive DTH skin reactions (categorical variable), as well as the number and percentage of patients with positive DTH skin reactions by visit will be presented for both the MIAS and IAS.

A summary of the number and percentage of patients with at least one positive T-cell response by Week 11 or 12 (main group) or by Week 13 (concomitant group) or by Week 8 (modified vaccination group), at the end of the treatment period with chemotherapy (modified vaccination group only), at Week 52, at end of study, and over entire study course will be presented for both the MIAS and IAS.

All details of DTH test and response will be listed, including derived variables.

A separate listing will present all details of immunological assessment, including derived variables. This listing will be sorted by site, patient, visit, and the standard operating procedure (SOP) version.

6.2 Survival Assessments

The secondary objective of the study is to assess at 2 years the clinical efficacy of GM-CSF/TG01. This will be assessed by two secondary efficacy endpoints:

- Disease–free survival (DFS)
- Overall survival (OS)

The ATP analysis set will be used to assess these endpoints.

A listing presenting the date of first IMP administration, date of surgery, date of first disease recurrence, date of death, DFS estimates and OS estimates (separately for time from date of first IMP administration and time from date of surgery) will be displayed for all treated patients. Censored DFS and OS observations will be flagged against each estimate.

6.2.1 Disease-free survival (DFS)

DFS is defined by two separate approaches:

- the number of weeks from first administration of IMP until the first documented disease recurrence or death from any cause and
- the number of weeks from surgery until the first documented disease recurrence or death from any cause.

DFS1 = [(the earliest of: first documented disease recurrence or death from any cause) – date of first IMP administration + 1] / 7.

DFS2 = [(the earliest of: first documented disease recurrence or death from any cause) – date of surgery + 1] / 7.

The first IMP administration is defined as the earliest date of:

- The start date of TG01 or GM-CSF administration or

- The start date of the chemotherapy regimen

Date of disease recurrence is defined as the earliest date of disease recurrence recorded on the Disease Assessment form in the eCRF. Date of death is recorded on the Statement of Death form in the eCRF.

It is expected (although not mandated) that a computed tomography (CT) scan will be performed every 6 months from start of IMP and if there is clinical evidence of disease recurrence.

If a patient has not had an event (disease recurrence or death) before the end of the 2-year follow-up, then DFS1 and DFS2 will be censored at the completion/withdrawal date.

If a patient withdrew participation in the study before disease recurrence or death then DFS1 and DFS2 will be censored at the date that they were last known to be recurrence free. If the patient has no post-IMP disease assessment, then DFS1 will be censored at the date of first IMP administration. If the patient has no post-surgery disease assessment, then DFS2 will be censored at the date of surgery.

For DFS1 the number and percentage of patients with events and censored will be summarised along with the minimum and maximum DFS1 time. Kaplan-Meier estimates of the 25th percentile, median and 75th percentile DFS1 time and their associated 95% confidence intervals (CIs) will also be presented. The table will also include the DFS1 rate and 95% CIs at 1,2 and 3 years, again estimated using Kaplan-Meier. DFS1 rate at 3 years will only be presented for the main, concomitant and main + concomitant groups. An identical summary will also be produced for DFS2.

Both DFS1 and DFS2 will also be presented graphically using a Kaplan-Meier plot and a swimmer plot.

Details of disease assessment will be listed.

6.2.2 Overall survival (OS)

OS is defined by two separate approaches:

- the number of weeks from first administration of IMP to death due to any cause and

- the number of weeks from surgery to death due to any cause.

OS1 = [(date of death from any cause) – date of first IMP administration + 1] / 7.

OS2 = [(date of death from any cause) – date of surgery + 1] / 7.

The first IMP administration is defined as the earliest date of:

- The start date of TG01 or GM-CSF administration or

- The start date of the chemotherapy regimen

Date of death will be recorded on the Statement of Death form in the eCRF.

If a patient has not had an event (death) before the end of the 2-year follow-up, then OS1 and OS2 will be censored at the completion/withdrawal date.

If a patient withdrew participation in the study before death then OS1 and OS2 will be censored at the date that they were last known to be alive.

For OS1 the number and percentage of patients with events and censored will be summarised along with the minimum and maximum OS1 time. Kaplan-Meier estimates of the 25th percentile, median and 75th percentile OS1 time and their associated 95% CIs will also be presented. The table will also include the OS1 rate and 95% CIs at 1,2 and 3 years, again estimated using Kaplan-Meier. OS1 rate at 3 years will only be presented for the main, concomitant and main + concomitant groups. An identical summary will also be produced for OS2.

OS1 and OS2 will also be presented graphically using a Kaplan-Meier plot and a swimmer plot.

Listing of the survival follow-up details will be presented.

6.2.3 Swimmer Plots

A swimmer plot will be produced, displaying the DFS1 and OS1 times for each patient including whether they experienced an event or were censored for each endpoint. This plot will be repeated for DFS2 and OS2 times.

6.3 Exploratory Analysis

6.3.1 Relationship between KRAS status and recurrence survival outcomes

The summaries of DFS1 and DFS2 will be presented by KRAS mutation detected (Yes/No) for the ATP analysis set.

DFS1 by KRAS mutation and DFS2 by KRAS mutation will also be presented graphically using a Kaplan-Meier plot.

6.3.2 CA19-9 levels and other biomarkers

Summary statistics of observed CA19-9 levels, absolute change from baseline and percentage change from baseline will be summarised by visit for the ATP analysis set. Baseline is defined as Day 1 CA19-9 result.

Individual patient CA19-9 values up to 1 year after first dose of IMP will be plotted, with separate figures for each group. Additionally, box plots will be produced to summarize values over time, with separate pages for each group.

All the blood collection details for CA19-9 including the result, will be listed with the blood collection details for the other biomarkers.

6.4 Examination of subgroups

The DFS and OS summaries and Kaplan-Meier plots (sections 6.2.1and 6.2.2) and CA19-9 levels tabulation (section 6.3.2) will be repeated for the subgroup of patients who received Gemcitabine only.

6.5 Interim analyses

An interim analysis (IA) will be performed when 1-year data are available for the Main and Concomitant groups.

The following tables and figures will be provided:

- Table 14.1.1 Patient disposition

- Table 14.1.2 Demography
- Table 14.1.3 Medical History of Pancreatic Cancer
- Table 14.1.4 KRAS Mutation Analysis
- Table 14.1.7 Prophylaxis
- Table 14.1.8.1 TG01 and GM-CSF Administration – Patient Level
- Table 14.1.9.1 Gemcitabine Administration –Patient Level
- Table 14.1.10.1. 5-FU and Leucovorin Administration –Patient Level
- Table 14.2.1.1 Immune Response (MIAS)
- Table 14.2.2.1 DTH Skin Test Reactions – By Study Period (MIAS)
- Table 14.2.3.1 DTH Skin Test Reactions – Overall (MIAS)
- Table 14.2.4.1 T-cell Responders (MIAS)
- Table 14.2.5.1 Disease-free Survival (DFS1) (ATP)
- Table 14.2.6.1 Disease-free Survival (DFS2) (ATP)
- Table 14.2.7.1 Overall Survival (OS1) (ATP)
- Table 14.2.8.1 Overall Survival (OS2) (ATP)
- Table 14.2.11.1 CA19-9 Values (U/ml) and Change from Baseline over Time
- All adverse event tables (Table 14.3.1 to Table 14.3.12 inclusive)
- Table 14.3.13.1 Haematology Values and Change from Baseline over Time
- Table 14.3.14.1 Biochemistry Values and Change from Baseline over Time
- Table 14.3.16.1 Summary of ECOG Performance Status over Time
- Figure 14.2.1.1 Kaplan-Meier Plot of Disease-free Survival (DFS1) (ATP)
- Figure 14.2.2.1 Kaplan-Meier Plot of Disease-free Survival (DFS2) (ATP)
- Figure 14.2.3.1 Kaplan-Meier Plot of Overall Survival (OS1) (ATP)
- Figure 14.2.4.1 Kaplan-Meier Plot of Overall Survival (OS2) (ATP)
- Figure 14.2.5 Swimmer Plot of Disease-free Survival (DFS1) and Overall Survival (OS1)
- Figure 14.2.6 Swimmer Plot of Disease-free Survival (DFS2) and Overall Survival (OS2)

When 1-year data is available for the Modified vaccination group and the Main and Concomitant groups have completed the study, a full set of TFLs will be produced based on all available data at that point.

6.6 Archival Listings

Investigator comments will be listed for all treated patients.

Statistical programming output used in preparing survival analysis will be provided in the archival output.

7   REFERENCES

Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, Schramm H, Fahlke J, Zuelke C, Burkart C, et al. *Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial.* JAMA. 2007;297:267–277.

Neoptolemos JP, Stocken DD, Bassi C, et al. *Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial.* JAMA. 2010;304:1073–81.

A Phase I/II Trial of TG01 and Gemcitabine as Adjuvant Therapy for Treating Patients with Resected Adenocarcinoma of the Pancreas

Targovax ASA Study No: CT TG01-01

Statistical Analysis Plan Addendum

Version: Final 1.0

Date: 04 October 2018

For Targovax ASA

If signing manually, please include: Signature + Date + Full Name + Position

Contents

LIST OF ABBREVIATIONS

ATP	All Treated Patients
DFS	Disease-free Survival
OS	Overall Survival
SAP	Statistical Analysis Plan

1   INTRODUCTION

This is an addendum to the final statistical analysis plan (SAP) dated 02 MAY 2018 documenting additional analyses following database lock. Full details of the changes are detailed below.

2   CHANGES TO THE FINAL SAP

2.1   Survival Assessments

These changes relate to section 6.2 of the final SAP.

As well as the previously planned derivation of DFS1, DFS2, OS1 and OS2 in weeks, these survival endpoints will also be derived in months.

All DFS1, DFS2, OS1 and OS2 summaries and graphical presentations will be repeated in months.

The listing of the survival data will include survival times in months.

For DFS1 and DFS2, survival rates and 95% confidence interval at 1, 2 and 3 years will not be presented. Instead, the number of patients who progressed at ≤ 1 year and at ≤ 2 years will be presented.

For OS1 and OS2, where survival rate is not calculated at 2 (or more) years due to there being no patient deaths, the survival rate for the previous year will be displayed instead.

The number of patients left at risk out of all patients in the group will be presented along with the survival rates.

Reason for the change

The addition of summaries in months will help with the interpretation of the results. Survival rates for DFS1 and DFS2 are not presented due to lack of data. OS1 and OS2 rates of the previous year will be presented as the current year's rate in the case described above to aid interpretation of the data.

2.2   Relationship between resection surgery outcome and survival endpoints

This change relates to section 6.3 of the final SAP.

Relationship between resection surgery outcome and survival endpoints will be investigated.

The summaries of DFS1, DFS2, OS1 and OS2 in weeks and months will be presented by resection surgery outcome (R0/R1) for the all treated patient (ATP) analysis set. These summaries will also be presented graphically using a Kaplan-Meier plot and a swimmer plot.

Reason for the change

This change explores a possible relationship between resection surgery outcome and survival endpoints.

2.3 Immune Response

This change relates to section 6.1. of the final SAP.

Definition of an immune response to GM-CSF/TG01 is updated to include the following condition:

Patients who have a positive immune response at Day 1 only and have no positive responses at any other visits will be excluded from both "initial treatment phase" and "over entire study course".

Reason for the change

This change was for clarification purposes.

2.4 Positive T-cell Responders

This change relates to section 6.1 of the final SAP.

Chemotherapy visits will also be considered in the derivation of positive T-cell responders.

Reason for the change

This change was for clarification purposes.

A Phase I/II Trial of TG01 and Gemcitabine as Adjuvant Therapy for Treating Patients with Resected Adenocarcinoma of the Pancreas

Targovax ASA Study No: CT TG01-01

Statistical Analysis Plan Addendum

Version: Addendum 2.0 Final 1.0

Date: 25 October 2018

For Targovax ASA

If signing manually, please include: Signature + Date + Full Name + Position

Contents

LIST OF ABBREVIATIONS

DTH   Delayed Type Hypersensitivity

IAS   Immune Analysis Set

MIAS   Modified Immune Analysis Set

1 INTRODUCTION

This is an addendum to the final statistical analysis plan (SAP) dated 02 MAY 2018 documenting additional analyses following database lock. Full details of the changes are detailed below.

2 CHANGES TO THE FINAL SAP

2.1 Immune Response

These changes relate to section 6.1 of the final SAP.

In addition to the reporting detailed in section 6.1 of the SAP, a summary table will present the number and percentage of patients in the categories below:

- Patients with an initial immune response by Week 11 or 12 (main group) or by Week 13 (concomitant group) or by Week 8 (modified vaccination group).

- Patients with an immune response during chemotherapy based on dates of chemotherapy treatment per patient (this will include immune assessments taken approximately 8 weeks after end of chemotherapy).

- Patients with an immune response post chemotherapy to week 50 (this will include immune response for end of study samples taken in the period after immune assessment taken approximately 8 weeks after end of chemotherapy and within week 50, by actual study dates).

- Patients with an immune response at week 52 (this includes week 51 – 53 by actual study dates).

- Patients with an immune response at the end of the study i.e. immune response after week 53, by actual study dates.

- Patients with at least one immune response over the entire study course.

Patients who discontinued from the study before the specific period will be classed as "Not applicable" and patients for which samples were not taken where they should have been will be classed as "Missing".

This table will be presented for both the MIAS and IAS population. The data will also be listed.

Reason for the change

The additional tables and listings will aid the interpretation of the data.